REMARKS

Claims 1, 2 and 6-15 are presently pending in the instant Application. No claim is amended by this Response.

Applicants gratefully acknowledge the withdrawal of the 35 U.S.C. §112 rejections of the previous Office action.

The Invention is Non-obvious

Claims 1, 2 and 6-15 are rejected under 35 U.S.C. §103(a), as being obvious over Iizuka et al. in view of Hara et al., Newgard et al. and Sedrani et al. The rejection is respectfully traversed.

The Office Action asserts that it would have been obvious to one of ordinary skill in the art to provide the assay of Iizuka et al. to detect the C-peptide in a sample such as recombinant insulin as taught by Newgard et al. because of the great demand in the field and C-peptide impurities are a common problem. The Office Action continues by asserting that it would have been obvious to modify Iizuka et al. with a non-radioactive tracer as taught by Sedrani and that optimizing the pH of Hara would have been obvious.

The deficiencies of Iizuka et al., Hara et al. and Newgard et al. are of record as discussed in Applicant's November 23, 2004 Response to the Office Action dated June 2, 2004, which

Response resulted in a withdrawal by the Office Action dated February 9, 2005 of the 35 U.S.C. §103(a) rejections in view of Iizuka et al. in view of Hara et al. and Newgard et al. In the instant Office Action, the rejection is raised again supported by Sedrani et al. and the unsupported conclusion that it would have been obvious to run the assay at a different pH.

This latter assertion is made without any reference to teach or suggest the pH change or even a reference that recognizes the problem that is solved by the instant invention. One reason the assay of the present invention is performed at a pH range of about 8.5 to about 9.0 is so that both HI and HIA1 remain dissolved during the whole incubation period and can be analyzed using the same assay without any variation, as described on page 5, lines 15-17 of the instant specification. The Office Action offers no reference to teach or suggest a) a suitable assay or b) that one could be developed to work at this pH range such that the antibodies used would interact with the antigens with sufficient affinity or c) a reference that suggested such an assay was even desirable. Accordingly, Applicants respectfully request an affidavit under 37 C.F.R. 1.104(d)(2) to support the Examiner's assertion that it would have been obvious to alter the reference teachings to modify the pH to the values claimed.

The addition of the Sedrani et al. reference does not solve the deficiencies of the previously applied Iizuka reference in view of Hara et al. and Newgard et al. All the Sedrani et al. reference allegedly teaches is the use of non-radioactive rapamycin tracer in a non-analogous assay art. Accordingly, Sedrani et al. does not solve the deficiencies of Iizuka et al., Hara et al. and

Newgard et al. in that it does not teach the use of non-radioactive labeling in C-peptide assays and as such is unrelated to the instant Invention and there is no motivation in any reference to combine Sedrani et al. with the other three references.

It is respectfully submitted that in making this rejection under 35 U.S.C. § 103(a), the Examiner has utilized impermissible hindsight in an unsuccessful attempt to construct the instant Invention from bits and pieces of these references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]." *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

The Office action continues by stating that Iizuka et al. do not teach (1) using recombinant human insulin as the sample, (2) non-radioactive assay to determine the C-peptide in a sample, and (3) conducting the assay in a pH of about 8.5 to about 9.0. However, those are not Iizuka's only deficiencies. Importantly, Iizuka et al. does not teach an assay using an antibody that can detect or determine a C-peptide-containing impurity comprising human C-peptide, monkey C-peptide or a mixture thereof in a sample of HI or derivatives. The antibody of the instant assay can detect human and/or monkey C-peptide and impurities containing either, as described on page 14, lines 18-20 of the specification. These are the requirements of an assay used to detect

the various C-peptide containing impurities potentially present in the manufacture of human insulin where, for example, the pre-pro-insulin is a chimeric human and monkey sequence. While the antibodies used in the present Invention are preferably raised against monkey C-peptide, that is not the end of the process. The thus raised antibodies were then further developed as described on page 7, lines 20-27. No reference of record teaches or suggests an assay using such a versatile antibody that can detect ***both*** human and monkey C-peptide and C-peptide containing impurities such as C-peptide linked to the A or B chain (but not the other) of HI and the PPI. Accordingly, Applicants respectfully submit that this 35 U.S.C. §103(a) rejection does not meet the criteria for a *prima facie* case of obviousness, that the Office Action uses impermissible hindsight to reconstruct only part of the instant Invention and accordingly, should be withdrawn. It is respectfully submitted that, for the foregoing reasons, claims 1 and 15 are allowable and as the remaining claims 2 and 6-14 are dependant on and only further limit claim 1, these claims are allowable as well for at least the same reasons that claim 1 is allowable.

Claim 13 is also rejected as being obvious under 35 U.S.C. §103(a) over Iizuka et al. in view of Hara et al., Newgard et al. and Sedrani et al. and in further view of Naithani et al. as Naithani et al. allegedly suggests using monkey C-peptide for comparative assay as compared to human C-peptide. This rejection is respectfully traversed.

The instant Invention is not claiming the use of monkey C-peptide in a comparative study. The instant Invention claims an assay that can detect monkey C-peptide in addition to human C-

peptide and impurities that contain either. The Naithani et al. reference does not teach or suggest the limitations in the pending Claims. Accordingly, this rejection under 35 U.S.C. §103(a) should be withdrawn.

In the light of the above, it is respectfully submitted that all objections be withdrawn, and the Claims be allowed to issue.

Fees

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account no. 18-1982.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks in the file history of the instant Application. The Claims are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

Mark C. Nelligan, Reg. No. 36,389

AVENTIS PHRAMACEUTICALS INC.
Patent Department D303A
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
Docket Number DEAV1999/LO67 US NP